Appendix A

Support in Application 08/966,506 for Presently Pending Claims Involving Coordinated Dosage Forms

U.S. 08/966,506 was filed on November 10, 1997 and issued as U.S. 6,077,539 on June 20, 2000. The '506 application is the parent of the present reissue application and it is Applicants' contention that it fully supports all of the pending claims involving coordinated dosage forms. These claims are as follows:

6. A pharmaceutical composition in unit dosage form suitable for oral administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such that the combination is effective in reducing or eliminating pain associated with said migraine headache and wherein said dosage form is coordinated.

7. The pharmaceutical composition of claim 6, wherein said unit dosage form is a tablet or capsule.

8. The pharmaceutical composition of claim 7, wherein said metoclopramide and said analgesic are in separate layers of a multilayer tablet.

9. The pharmaceutical composition of claim 6, wherein said unit dosage form is substantially free from any 5 HT agonist vasoactive agent.

10. The pharmaceutical composition of claim 6, wherein said analgesic is an NSAID.

11. The pharmaceutical composition of claim 10, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition of claim 11, wherein said NSAID is naproxen.

13. The pharmaceutical composition of claim 10, wherein said NSAID is long acting or is formulated to be long acting.

14. A method of increasing the rate of absorption of a drug into the bloodstream of a patient, wherein rate of absorption is the time from which the drug is administered until the time that it reaches a peak plasma concentration, comprising:

administering said drug together with metoclopramide in a coordinated dosage form, wherein said metoclopramide is administered in an amount effective to increase gastric motility and wherein said drug is administered in a therapeutically effective amount.

15. The method of claim 14, wherein said patient is in a state of gastric stasis at the time said drug and said metoclopramide are administered.

16. The method of claim 14, wherein said drug is administered for the treatment of migraine headache.

17. The method of claim 14, wherein said drug is an analgesic.

18. The method of claim 14, wherein said drug is an NSAID.

19. The method of claim 18, wherein said NSAID is long acting or is formulated to be long acting.

20. The method of claim 18, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein said NSAID is naproxen.

22. A pharmaceutical composition in unit dosage form suitable for oral administration in the treatment of migraine headache, comprising:

(a) metoclopramide in an amount effective to increase gastric motility in a patient; and

(b) a non-acidic analgesic in an amount effective to reduce or eliminate pain associated with said migraine headache;

and wherein said unit dosage form is coordinated.

23. The pharmaceutical composition of claim 22, wherein said unit dosage form is a tablet or capsule.

24. The pharmaceutical composition of claim 22, wherein said unit dosage form is substantially free of any 5 HT agonist vasoactive agent.

25. The pharmaceutical composition of claim 22, wherein said analgesic is a long acting NSAID.

26. The pharmaceutical composition of claim 22, wherein said analgesic is a cyclooxygenase-2 inhibitor.

27. The pharmaceutical composition of claim 26, wherein said cyclooxygenase-2 inhibitor is celecoxib.

28. The pharmaceutical composition of claim 27, wherein said celecoxib is present in an amount of between 25 and 250 mg and said metoclopramide is present in an amount of between 1 mg and 100 mg.

29. The pharmaceutical composition of claim 22, wherein said analgesic is formulated to be long acting.

35. A pharmaceutical composition in unit dosage form suitable for oral administration to a human for the treatment of migraine headache, comprising: metoclopramide and an analgesic, present in an amount such that the combination is effective in reducing or eliminating pain associated with said migraine headache, wherein said dosage form is an acid-base storage stabilized dosage form and wherein said unit dosage form is coordinated.

36. The pharmaceutical composition of either claim 34 or 35, wherein either said metoclopramide or said analgesic is barrier coated.

37. The pharmaceutical composition of either claim 34 or 35, wherein said unit dosage form is substantially free of any 5 HT agonist vasoactive agent.

38. The pharmaceutical composition of either claim 34 or 35, wherein said analgesic is an NSAID.

39. The pharmaceutical composition of claim 38, wherein said NSAID is selected from the group consisting of: acetaminophen; ibuprofen; flurbiprofen; ketoprofen; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; nabumetane; piroxicam; celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; and NS398; or a pharmaceutically acceptable salt thereof.

40. The pharmaceutical composition of claim 39, wherein said NSAID is naproxen.

41. The pharmaceutical composition of claim 38, wherein said NSAID is long acting or is formulated to be long acting.

Overall, the claims can be divided into 3 categories: a) composition claims involving the use of coordinated unit dosage forms (6-13 and 22-29); b) composition claims involving the use of unit dosage forms that are *both* coordinated and acid base stabilized (35-41);[1] and c) methods of using dosage forms that are coordinated (claims 14-23). The broadest of the composition claims are 6 and 22 which are both directed to coordinated pharmaceutical compositions in unit dose form. The claims are of similar scope except that claim 22 specifies the presence of a non-acidic analgesic. Claims 7-13 are dependent on claim 6 and claims 23-29 are dependent on claim 22. These dependent claims add a variety of limitations with respect to: a) the particular type of dosage form used (claims 7, 8 and 23); b) the absence of 5

[1] Dependent claims 36-41 refer back both to claim 35 and to claim 34. The latter is directed to multilayer dosage forms that are acid-base storage stabilized.

HT agonist vasoactive agents (claims 9 and 24); and the particular analgesic used (claims 10-13 and 25-29).[2]

Claim 35 is independent and is broadly directed to pharmaceutical compositions in unit dosage forms that are acid base-storage stabilized and coordinated. Dependent claims limit this composition with respect to: a) the presence of a barrier coating (claim 36); b) the absence of a 5HT vasoactive agonist (claim 37); and with respect to the particular analgesic present (claims 38-41).

Claim 14, the only independent method claim, is directed to a method for increasing the rate of absorption of drug into the bloodstream of a patient using a coordinated dosage form containing the drug together with metoclopramide. Dependent claims specify: a) administration during gastric stasis (claim 15); b) treatment for migraine headache (claim 16); and c) the specific drug or type of drug combined with metoclopramide (claims 17-21).

Support in 08/966,506

The '506 application issued as US 6,077,539 on June 20, 2000. Since it should be readily available to the Examiner, the cites below are to made with reference to this patent. The same text may be found in the application as filed.

A. Support for Claims Broadly Encompassing Coordinated Pharmaceutical Compositions (Relevant to Claims 6, 14, 22 and 35)

Col. 10, lines 36-49 (Definition of Coordinated):

> F. "Coordinated" in the practice of the present invention refers to administration of metoclopramide and at least one NSAID, wherein the metoclopramide is available in at least effective local gastrointestinal concentration in or at the gastrointestinal tract of a subject within at least about 1 to 30 minutes after administration and particularly about 5 minutes or less after administration, and more particularly about 3 minutes or less, and at least one NSAID will be initially available at a therapeutically effective level in a subject from at least about 30-60 minutes, and preferably from at least about 5 to 60 minutes, and continuing to about 12-24 hours after administration, but also wherein the therapeutically effective level of said NSAID is

[2] One of these dependent claims (28) serves to restrict a specified analgesic to particular dosages.

not attained until after metoclopramide is present in effective local gastrointestinal concentration.

Particularly note that coordinated unit dosage form is a dosage form that, upon administration provides the sequential delivery of the dosages as noted herein. Coordinated differs from co-timely in that coordinated is more specific as to the sequence in which specific drug levels are obtained.

Col. 10, lines 56-57 (coordinated unit dosage forms):

Particularly note that coordinated unit dosage form is a dosage form that, upon administration provides the sequential delivery of the dosages as noted herein.

Col. 7, line 66- col. 8, line 11:

It has now been discovered that coordinated and co-timely administration of less of[3] metoclopramide and a long acting non-steroidal anti-inflammatory drug (NSAID) therapeutically combined in a single layer tablet, bilayer tablet, or multilayer tablet for oral administration and possessing unique and specific formulation and dissolution characteristics provides an enhanced non-vasoactive therapeutic effect and relieves the symptoms of migraine, including, but not limited to headache pain and nausea, in patients in a superior manner to each individual component administered as a sole agent by use of a conventional tablet(s) of currently available products. Naproxen sodium is one such long acting NSAID. In particular embodiments, however, NSAID's other than long-acting NSAIDs are useful.

Additional Support for Claim 14 (method for increasing rate of absorption):

Col. 4, lines 55-67:

The intended therapeutic result, i.e., rapid, complete, and long-lasting migraine symptom relief, is produced with a unit dosage form that allows the metoclopramide component to dissolve first and extremely quickly, followed within a few minutes by the rapid dissolution and absorption of the naproxen sodium component. Particular excipients, compaction pressures and particles affect such mobilization, and particular note is made of naproxen sodium crystals in the 10 μm to 200 μm range (more particularly about 90

[3] The words "less of" appear to be a typographical error. The specification indicates that metoclopramide may vary from 1 mg up to 30 mg (see col. 6, lines 43-48). The actual dosage of metoclopramide (in the form of its hydrochloride salt) used in the Examples was 8 mg or 16 mg. The amount of the hydrochloride salt of metoclopramide in dosage forms known in the art is discussed in col. 8, lines 55-65 and appears to generally be 5-10 mg.

μm to about 150 μm) which particle sizes assist in permitting rapid absorption. Such a dosage form speeds the absorption of both active ingredients producing an enhanced therapeutic effect in the treatment of migraine.

Col. 6, lines12-21:

This invention further comprises a non-vasoactive, supra-vasoactive syndrome minimized method of therapeutic treatment of migraine in a human comprising co-timely administering metoclopramide in at least about an effective local gastrointestinal amount, and, further administering at least one long acting NSAID in a therapeutically effective amount, and wherein no 5HT agonist vasoactive agents are administered, optionally in unit dosage form. Particular note is made of this method wherein administering of metoclopramide is coordinated administering with said NSAID.

Col. 14, lines 43-48:

In this context, the combination of metoclopramide and a long-acting NSAID in a single layer tablet or other solid dosage form, or in a bi- or multi layer tablet of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the NSAID, and provides an enhanced therapeutic effect against migraine symptoms in patients.

Col. 15, lines 14-21:

In this context, the combination of metoclopramide and a long-acting NSAID in a single layer tablet or other solid dosage form, or in a bi- or multi layer tablet of the type described in this invention relieves nausea, improves gastrointestinal motility which enhances the speed of absorption of the NSAID, and provides an enhanced therapeutic effect against migraine symptoms in patients.

Additional Support for Claim 35 (coordinated dosage forms that are acid-base storage stabilized)

Col. 7, lines 33-41:

In yet another embodiment the invention includes method of rapidly introducing an NSAID administered via oral administration into the small bowel of a subject in gastric stasis by the step of administering oral metoclopramide in effective local gastrointestinal concentration in a co-timely coordinated non-spiking acid-base stable unit dosage form further including said NSAID. Particular reference is mad to naproxen including naproxen sodium and metoclopramide from about 5 to about 10 mg.

Col. 13, lines 9-17:

> A particular type of unit dosage form is an "acid-base storage stable" unit dosage form. "Acid-base storage stable" unit form shall mean a dry unit dosage form of metoclopramide (a Lewis base, whether in the form of a free base or as an acid salt) in a tablet with an acid form of an NSAID wherein the potency of either active ingredient is not reduced by more than about 15% in 21 days storage at ambient temperature (15°-20° C), nor by more than about 5% in 14 days.

B. Use of Specific Analgesics Including Naproxen (Relevant to claims: 10-13;17-21; 25-29; and 38-41)

Col. 5, lines 35-40:

> As to the NSAID of the dosage form it is selected from the group comprising flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, nabumetane, mefenamic, piroxicam, or pharmaceutically acceptable salt thereof, with particular reference to naproxen and naproxen sodium.

Col. 5, lines 49-51:

> A noted dosage form is naproxen sodium comprising from about 200 to about 600 mg, and the metoclopramide comprising from about 3 to about 30 mg.

Col. 6, lines 28-32:

> NSAIDs of note in this method are selected from the group comprising flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, nabumetane, mefenamic, piroxicam, or pharmaceutically acceptable salt thereof, with specific not of naproxen and naproxen sodium.

C. Use of Multilayer Tablet with Drugs Segregated to Different Layers (Relevant to claim 8)

Col.5, line 58-61:

> One bilayer dosage form comprises a first layer and a second layer, and wherein the naproxen sodium is only in the first layer and metoclopramide is only in the second layer.

Col.6, lines 56-59

> Examples of dosage forms of this method included a bilayer dosage form of a first layer and a second layer, and wherein the naproxen

sodium is only in the first layer and said metoclopramide is only in the second layer.

D. Administration of Unit Dosage Form to Patient in Gastric Stasis (Relevant to claim 15)

Col. 7, lines 33-41:

> In yet another embodiment the invention includes method of rapidly introducing an NSAID administered via oral administration into the small bowel of a subject in gastric stasis by the step of administering oral metoclopramide in effective local gastrointestinal concentration in a co-timely coordinated non-spiking acid-base stable unit dosage form further including said NSAID. Particular reference is mad to naproxen including naproxen sodium and metoclopramide from about 5 to about 10 mg.

E. Use of Long Acting NSAIDs (Relevant to claims 13; 19; 25; 29; and 41)

see Col. 7, line 66-col. 8, line11 (quote shown above):

see also col. 8, lines 15- 30 for definition of long acting NSAIDs

F. Dosage Forms in the Form of a Tablet or Capsule (Relevant to claims 7 and 23)

Col. 12, lines 52-56:

> N. "Unit dosage form" shall mean single drug administration entity. By way of example, a single tablet, capsule, dragee, or trochee (oral unit dosage forms), suppository, or syringe combining both metoclopramide and an NSAID would be a unit dosage form.

G. Treatment of Migraine Headache (Relevant to claim 16)

see Treatment Examples 1-4, col 20, line 30- col. 21, line 17.

H. Use of Barrier Coating for Acid-Base Storage Stabilization (Relevant to claim 36)

Col. 16, lines 27-41: (part of Tablet Example 1)

> Thus, separation between the component active ingredients can be obtained by presenting either or both active ingredients in barrier

coated form. In view of the importance of rapid availability of metoclopramide in a therapeutically effective dosage, an embodiment in which only the NSAID is barrier coated is noted. Suitable barrier type coating materials for naproxen sodium include OpaDry as is applied in combination with water for irrigation and talc. Other materials are shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and cellulose acetate phthalate. Thin coatings, on the order of about 25-250 microns retards the availability of naproxen by no more than about 5 minutes, while substantially extending storage life of the combined formulation.

I. Absence of 5 HT Vasoactive Agents in Formulations and Methods (Relevant to claims 9; 24; and 37)

Col. 5, lines 18-27:

> This invention comprises a non-vasoactive, supra-vasoactive syndrome ("SVS") minimized dosage form for treatment of migraine in a human comprising (i) rapid availability metoclopramide in at least about an effective local gastrointestinal amount, and, (ii) at least one long acting NSAID in a therapeutically effective amount, (iii) wherein said dosage form is a coordinated dosage form, and (iv) wherein the dosage form is absent 5HT agonist vasoactive agents. In particular embodiments, an acid base storage stable dosage form is noted.

Col. 6, lines 12-21:

> This invention further comprises a non-vasoactive, supra-vasoactive syndrome minimized method of therapeutic treatment of migraine in a human comprising co-timely administering metoclopramide in at least about an effective local gastrointestinal amount, and, further administering at least one long acting NSAID in a therapeutically effective amount, and wherein no 5HT agonist vasoactive agents are administered, optionally in unit dosage form. Particular note is made of this method wherein administering of metoclopramide is coordinated administering with said NSAID.